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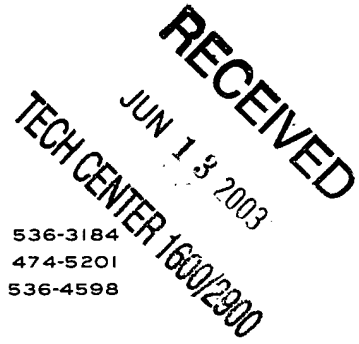

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June 9, 2003 — Date

Steven L. Highlander

Commissioner for Patents
Alexandria, VA 22313-1450

RE: *U.S. Patent Application No. 09/922,490 entitled "ENHANCED EXPRESSION OF TRANSGENES" - Richard J. Cristiano AND Dao Nguyen*
(Client reference: MDA95-040CON1)

Sir:

Please find enclosed:

(1) A Response to Office Action dated March 11, 2003 with Appendices A-D; and

(2) A return postcard to acknowledge receipt of these materials. Please date stamp and mail this postcard.

Should any fees be required under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the enclosed materials, the Commissioner is authorized to deduct fees from Fulbright & Jaworski Deposit Account No.: 50-1212/INRP:021USC1/SLH.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642

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Encl: as noted

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Richard J. Cristiano and Dao Nguyen

Serial No.: 09/922,490

Filed: August 3, 2001

For: ENHANCED EXPRESSION OF TRANSGENES

Group Art Unit: 1632

Examiner: D. T. Nguyen

Atty. Dkt. No.: INRP:021USC1

RESPONSE TO OFFICE ACTION DATED MARCH 11, 2003

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Commissioner:

This paper is submitted in response to the Office Action dated March 11, 2003, for which the three-month date for response is June 11, 2003. It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10106882/SLH.

Reconsideration of the application in view of the following amendments and remarks is respectfully requested.

I. AMENDMENT

Please cancel claim 2, and amend the claims as follows:

1. (Amended) A method for enhancing the expression of a transgene in a dividing cell comprising:

(a) contacting said dividing cell with a DNA-damaging agent; and

(b) transferring said transgene into said dividing cell between greater than about 1 day and less than or equal to 4 days after contacting said dividing cell with said DNA damaging agent.

7. (Amended) The method of claim 1, wherein said transgene is transferred at about 2 days after contacting said dividing cell with said DNA-damaging agent.

9. (Amended) The method of claim 1, wherein said transgene is a tumor suppressor gene.

10. (Amended) The method of claim 9, wherein said tumor suppressor gene is p53.

12. (Amended) The method of claim 11, wherein said promoter is a CMV IE promoter.

16. (Amended) The method of claim 1, wherein said contacting of said DNA-damaging agent with said dividing cell is discontinued and wherein said transgene is transferred into said

dividing cell between greater than about 1 day and less than or equal to 3 days after said contacting of said DNA-damaging agent with said dividing cell is discontinued.

Please add the following new claims:

17. (New) A method for enhancing the expression of a transgene in a target neoplastic cell *in vivo*, comprising:

(a) administering a DNA-damaging agent to a subject containing a target neoplastic cell; and

(b) transferring said transgene into said target cell between greater than about 1 day and less than or equal to 4 days after said administering step.

18. (New) The method of claim 17, wherein said tumor cell is cisplatin sensitive.

19. (New) The method of claim 17, wherein said tumor cell is cisplatin insensitive.

20. (New) The method of claim 17, wherein said DNA-damaging agent is selected from the group consisting of cisplatin, carboplatin; VP16, teniposide, daunorubicin, doxorubicin, dactinomycin, mitomycin, plicamycin, bleomycin, procarbazine, nitrosourrea, cyclophosphamide, bisulfan, melphalan, chlorambucil, ifosfamide, merchloroehtamine, and ionizing radiation.

21. (New) The method of claim 17, wherein said transgene is transferred at about 2 days after contacting said target cell with said DNA-damaging agent.

22. (New) The method of claim 17, wherein said transfer of said transgene is accomplished by a technique selected from the group consisting of liposome-mediated transfection, receptor-mediated internalization and viral infection.

23. (New) The method of claim 17, wherein said transgene is a tumor suppressor.

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24. (New) The method of claim 23, wherein said tumor suppressor is p53.

25. (New) The method of claim 24, wherein said p53 transgene is under the transcriptional control of a promoter.

26. (New) The method of claim 25, wherein said promoter is a CMV IE promoter.

27. (New) The method of claim 26, wherein said transgene is regulated by a polyadenylation signal.

28. (New) The method of claim 27, wherein said polyadenylation signal is an SV40 polyadenylation signal.

29. (New) The method of claim 28, wherein said p53 transgene is carried in an adenoviral vector.

30. (New) The method of claim 17, wherein said DNA-damaging agent is removed from said cell and wherein said transgene is transferred into said target cell between greater than about 1 day and less than or equal to 3 days after removing said DNA-damaging agent.

31. (New) A method for enhancing the expression of a transgene in a target neoplastic cell *in vitro*, comprising:

(a) contacting said target neoplastic cell with a DNA-damaging agent;

(b) transferring said transgene into said neoplastic cell between greater than about 1 day and less than or equal to 4 days after said contacting step, whereby expression of the transgene is enhanced as the result of the treatment of said target neoplastic cell with said DNA-damaging agent.

32. (New) The method of claim 32, further comprising removing said DNA-damaging agent from said cell and transferring said transgene into said target neoplastic cell between greater than about 1 day and less than or equal to 3 days after removing said DNA damaging agent.

33. (New) The method of claim 32, wherein said tumor cell is cisplatin insensitive.

34. (New) The method of claim 32, wherein said DNA-damaging agent is selected from the group consisting of cisplatin, carboplatin; VP16, teniposide, daunorubicin, doxorubicin,

dactinomycin, mitomycin, plicamycin, bleomycin, procarbazine, nitrosourrea, cyclophosphamide, bisulfan, melphalan, chlorambucil, ifosfamide, merchloroehtamine, and ionizing radiation.

35. (New) The method of claim 32, wherein said transgene is transferred at about 2 days after contacting said target cell with said DNA-damaging agent.

36. (New) The method of claim 32, wherein said transfer of said transgene is accomplished by a technique selected from the group consisting of liposome-mediated transfection, receptor-mediated internalization and viral infection.

37. (New) The method of claim 32, wherein said transgene is a tumor suppressor.

38. (New) The method of claim 37, wherein said tumor suppressor is p53.

39. (New) The method of claim 38, wherein said p53 transgene is under the transcriptional control of a promoter.

40. (New) The method of claim 39, wherein said promoter is a CMV IE promoter.

41. (New) The method of claim 40, wherein said transgene is regulated by a polyadenylation signal.

42. (New) The method of claim 41, wherein said polyadenylation signal is an SV40 polyadenylation signal.

43. (New) The method of claim 42, wherein said p53 transgene is carried in an adenoviral vector.

44. (New) The method of claim 32, wherein said DNA-damaging agent is removed from said cell and wherein said transgene is transferred into said target cell between greater than about 1 day and less than or equal to 3 days after removing said DNA-damaging agent.

45. (New) The method of claim 16, wherein said contacting of said DNA-damaging agent with said target cell is discontinued by ceasing administration of said DNA-damaging agent.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

The Action acknowledges the amendment of claims 1, 6, and 7, and the addition of claim 16 by the Amendment filed December 26, 2002. The Action also acknowledges Applicants' election, without traverse, of the species of cisplatin and viral infection in the Response to Election of Species Requirement filed December 26, 2002. Therefore, claims 1-16 were pending at the time of the Action. Claims 1, 7, 9, 10, 12, and 16 have been amended in the Amendment contained herein. Claim 2 has been canceled. Claims 17-45 have been added. Therefore, claims 1 and 3-45 are presently pending. A copy of the amended claims with editing indicia is attached as Appendix A. A clean copy of the presently pending claims is attached as Appendix B.

B. Rejections Under 35 U.S.C. §112, First Paragraph, are Overcome

1. Addition of Claims in Accordance with Examiner's Agreement of What is Enabled

Claims 1-16 are rejected under 35 U.S.C. §112, first paragraph, as not enabled. The Examiner acknowledges that the specification is enabling for:

I. A method for enhancing the expression of a transgene in a target neoplastic cell *in vivo* comprising:

(a) administering a DNA-damaging agent to a subject containing a target neoplastic cell; and

(b) transferring said transgene into said target neoplastic cell between 1-4 days after said administering step;

II. A method for enhancing the expression of a transgene in a target neoplastic cell *in vitro* comprising:

(a) contacting said target neoplastic cell with a DNA-damaging agent;

(b) transferring said transgene into said neoplastic cell between about 1-4 days after said contacting step, whereby expression of the transgene is enhanced as the result of the treatment of said target neoplastic cell with said DNA-damaging agent; and

III. The method of II, wherein said DNA-damaging agent is removed from said cell and wherein said transgene is transferred into said target cell between about 1-3 days after removing said DNA damaging agent. See Office Action, page 2-3.

New claim 17 has been added to track the language of claim I suggested in the Action. As the Action acknowledges that new claim 17 is enabled, Applicants submit that new claim 17, and dependent claims 18-31, which incorporate the limitations of claim 17, satisfy the enablement requirements of §112, first paragraph.

New claim 31 has been added to track the language of claim II suggested in the Action. In addition, new claim 32 has been added to track the language of claim III suggested in the Action. As the Action acknowledges that new claims 31 and 32 are enabled, Applicants submit that these claims, and new dependent claims 33-44, which incorporate the limitations of claim 31, satisfy the enablement requirements of §112, first paragraph. With regard to the new claims, Applicants draw the Examiner's attention to the narrowing of the timing limitation, which is discussed below in the response to the rejections under 35 U.S.C. §102(e).

2. The Specification Enables the Claimed Invention

According the the Examiner, the specification does not reasonably provide enablement for: (1) *in vitro* and/or *in vivo* methods for enhancing the expression of a transgene in target cells other than neoplastic cells by using any DNA-damaging agent; and (2) methods for enhancing the expression of a transgene *in vivo* wherein the step of removing a DNA damaging agent from an *in vivo* target cell treated with the DNA damaging agent is employed. In support of this contention, the Examiner cites Applicants' statement in the last paragraph of page 6 of the Specification, and the Son *et al.* references (PNAS, 19:12669-12672, 1994). Applicants respectfully traverse this rejection.

a. The Specification is Enabling for Use of Target Cells other than Neoplastic Cells

According to the Examiner, the following statement from the Specification indicates that the Specification is not enabling for target cells other than neoplastic cells:

> "The present invention relies on the observation that treatment of neoplastic cells with DNA-damaging agents, prior to transduction with a transgene, results in the enhanced expression of the transgene. This effect is not observed when the cell is not neoplastic, *i.e.*, when the cell exhibits normal growth control." Specification, page 6, lines 27-30.

Applicants disagree with the Examiner's contention that Specification does not enable for cells other than neoplastic cells. First of all, the Specification provides ample indication that cells other than neoplastic cells are contemplated by the present invention. In particular, Applicants have indicated that "the invention provides for the enhancement of gene expression by providing a DNA damaging agent, preferably to a dividing cell, prior to administration of a vector containing a gene or genes of interest." Specification, page 2, line 32 through page 3, line 2 (emphasis added). In addition, "[t]he target cell preferably is a dividing cell, and more preferably is a tumor cell." Specification, page 3, lines 8-9. Thus, the Specification clearly contemplates use of cells other than neoplastic cells.

Applicants draw the Examiner's attention to the amendment of claim 1, wherein the term "target cell" has been replaced with the term "dividing cell." Claim 2 has been canceled since it would be a duplicate of claim 1.

When rejecting a claim under the enablement requirement of 35 U.S.C. §112, "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-

62, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). As noted by the Federal Circuit, "this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." *Id.*

Applicants assert that the Examiner has not met the initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by the claims is not adequately enabled by the Specification, and that no sufficient reason has been providing for doubting why the Specification is not enabling. Applicants assert that the Specification as written clearly provides support for enablement of the claimed invention as it relates to dividing cells, including neoplastic cells.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See *In re Wands,* 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir., 1988).

Without conceding that the claims as originally written were not enabled, Applicants assert that their Specification enables the invention all of the claims in view of the amendments to the claims, which now pertain to "dividing cells." In particular, as agreed by the Examiner, the application indicates and demonstrates that prior treatments of host cells with a DNA-damaging agent followed by the steps of removing the DNA-damaging agent from the host cells and transfecting the host cells with a transgene, results in improved expression of the transgene when compared to simultaneous or subsequent treatment with a DNA-damaging agent, or no DNA-damaging agent at all. Specification, page 7, lines 18-28; Example 1, page 38, line 4 through page 44, line 24; and Example 2, page 45, line 1 through page 50, line 28. The

Specification also provides factual evidence, as noted by the Examiner, demonstrating *in vivo* cisplatin (CDDP)-induced enhancement of transgene expression, wherein the transfection step is employed at 0, 2, 4, and 6 days following intraperitoneal injection of CDDP to nude mice. Specification, Example 1, page 38, line 4 through page 44, line 24. The Specification also provides evidence showing sensitizing effectors of DNA damaging agents other than cisplatin (etoposide and ionizing radiation) when a gene transfection step was employed at 1, 2, and 4 days following the washing of tumor cells contacted by the DNA-damaging agent. Example 1, page 38, line 4 through page 44, line 24 and FIG. 3. Thus, Applicants assert that there is substantial information supporting enablement of the claims in the specification.

The Examiner's concerns that the Specification does not specifically teach *in vitro* and/or *in vivo* methods for enhancing the expression of a transgene in cells other than a neoplastic cells should not result in lack of enablement of the invention as claimed. Applicants assert that their working examples in the Specification pertaining to use of neoplastic cells bears a clear correlation to the entire scope of each claim as it pertains to dividing cells, and as a result, the enablement requirement is satisfied.

Nor should the fact that some experimentation may be involved to make and/or use the claimed invention be dispositive. The test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Any experimentation required to practice the claimed invention as it pertains to use of cells other than neoplastic cells, in view of the disclosure in the specification and the level skill of an ordinary artisan, would certainly not be undue experimentation.

According to the Examiner, Son *et al.* teaches that "muscles of the cisplatin-treated animals did not express higher CAT activity than the muscles from control uninjected animals," and that "the enhanced sensitivity to lipofection seems to be limited to the tumor cells of the cisplatin-treated animals." (pages 12671, column 2, third paragraph). The Examiner cites this reference for the assertion that the Specification is not enabling for target cells other than neoplastic cells.

However, the disclosure of Son *et al.* has no relevance to the instant invention. In Son *et al.*, the DNA-damaging agents were administered to tumors one week prior to lipofection. See abstract of Son *et al.* The instant specification discloses that the enhancement effect of DNA-damaging agents on transgene expression is short-lived, "as the percentage of positively stained, [*in vitro*] treated cells, infected on day 4 or 5 after CDDP exposure was similar to that of the control." Specification, page 42, lines 6-8. Similarly, transgene expression was substantially enhanced when the transgene was delivered at 2 and 4 days after *in vivo* administration of CDDP, but was only slightly enhanced at 6 days after administration. Specification, page 44, lines 19-24.

Son *et al.* failed to deliver the transgenes during the time period when a substantial enhancement of expressed would be expected. This is demonstrated by the instant Specification, which shows that etoposide is effective at enhancing transgene expression. Specification, page 43, lines 20-23. To the contrary, Son *et al.* reported no effect of etoposide on lipofection. The skilled artisan, reading the instant specification in light of Son *et al.*, would conclude that Son *et al.* was examining a different phenomenon than that disclosed in the present application, and that the findings of Son *et al.* pertaining to the effects in muscle cells have no relevance to the instant application.

In view of the above, the Specification clearly enables the claimed invention as it pertains to use of target cells other than neoplastic cells.

b. The Specification is Enabling for Discontinuation of Contact of the DNA-Damaging Agent with the Target Cell

The Examiner states that the claimed invention is not enabled because "the step of removing the DNA-damaging agents from cells contacted by the DNA-damaging agents is employed," and the Specification fail to "provide sufficient guidance and/or factual evidence as to how the *in vivo* removal step is employed without undue experimentation by a skilled artisan." Office Action, page 5, paragraph 2.

Without conceding that the claims as originally written are not enabled in this regard, Applicants draw the Examiner's attention to present claim 16, which indicates that "contact of said DNA-damaging agent with said target cell is discontinued." Discontinuation of contact of a DNA-damaging agent with a target cell is distinct from removing the DNA-damaging agent from a target cell. Indeed, the Examiner apparently agrees that "the step of stopping an *in vivo* administration of DNA-damaging agents [sic] to an animal prior to the *in vivo* gene transfer step is not the same as the step of actively removing contacted DNA-damaging agents from target tumor cells of the animal." Office Action, page 5, paragraph 2.

In this regard, Applicants assert that the Specification is sufficiently enabling for discontinuation of contact of a DNA-damaging agent with a cell. With regard to the discontinuation of a DNA-damaging agent, the Specification teaches that contacting of a DNA-damaging agent with a target cell may be discontinued by ceasing administration of a DNA-damaging agent. In particular, the Specification teaches that:

> "[p]referably, the *in vitro* administration of the DNA-damaging agent precedes the transduction of the host cell by about 1-3 days (about 24-72 hours) and, more preferably, about 2 days (48) hours after removal of the agent. *In vivo*, the time frame may be delayed somewhat, depending on the type and route of administration. Thus, it is suspected that a systemic administration of a chemotherapeutic should precede provision of the transgene by 2-4 days (about 48-96 hrs) and, more preferably, about 3 days (72 hrs)." Specification, page 7, lines 22-28.

Therefore, one of skill in the art would understand that discontinuation of contact of a DNA-damaging agent with a target cell may refer to ceasing of administration of a DNA-damaging agent to a target cell. Thus, the time interval specified in the claimed invention may be measured from the time the administration of the DNA-damaging agent is discontinued. In this regard, new dependent claim 45, which contemplates completion of administration of a DNA-damaging agent as an example whereby contact of a DNA-damaging agent with a target cell is discontinued, has been added.

In addition, the Specification teaches that contacting of a DNA-damaging agent with a target cell *in vivo* may also be discontinued by ceasing administration of ionizing radiation. Specification, page 12, lines 24-28; Example 1, page 43, lines 12-14, and FIG. 3.

The Specification also teaches that contacting of a DNA-damaging agent with a target cell may also be discontinued by washing the DNA-damaging agent from a host cell. Example 1, page 38, line 4 through page 44, line 24 and FIG. 3. The Examiner admits that "the specification states the step of removing a DNA-damaging agent from a host cell is accomplished by washing DNA-damaging agent-incubated cells with a buffer solution prior to the transfection step." Office Action, page 4, paragraph 1, citing Specification, page 39, lines 12 and 13.

As discussed *supra*, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504. Any experimentation required to practice the claimed invention as it pertains to the discontinuation of contact of a DNA-damaging agent with a target cell for *in vitro* and *in vivo* methods, in view of the disclosure in the Specification and the level skill of an ordinary artisan, would certainly not be undue experimentation.

Applicants assert that the Specification does not need to disclose each and every method by which contact of a DNA-damaging agent with a target cell is discontinued. See *In re Fisher*, 427 F.2d 833, 166 U.S.P.Q. 18 (C.C.P.A. 1970). The Specification clearly discloses multiple methods by which contact of a DNA-damaging agent with a target cell can be discontinued, and these methods clearly bear a reasonable relationship to the scope of the claimed invention.

Applicants assert that they have met their burden by presenting persuasive arguments and suitable proof sufficient to show that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973). Accordingly, Applicants respectfully request that the rejection of claims 1-16 under 35 U.S.C. §112, first paragraph, be withdrawn.

C. Rejections Under 35 U.S.C. §112, Second Paragraph, are Overcome

Claims 1-15 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Claim 1 and claims dependent therefrom are said to be indefinite in the recitation of "a method for enhancing the expression of a transgene" because it is not apparent as

to exactly where "the expression of a transgene" occurs. In this regard, Applicants have amended claim 1 to indicate that the expression of a transgene occurs in a dividing cell.

According to the Examiner, the recitation of "said transgene is a tumor suppressor" in claim 9 is indefinite because it is not apparent how a transgene, which is a DNA sequence, is a tumor suppressor, which is a protein. Accordingly, claims 9 and 10 have been amended to indicate that "tumor suppressor" refers to "tumor suppressor gene."

The Examiner also indicates that the term "the CMV IE promoter" in claim 12 lacks an antecedent basis because not all CMV IE promoters known in the prior art are identical in their structural sequences, and thus, it is not apparent as to which of the CMV IE promoters the term refers to in this regard. Applicants have amended claim 12 to change "the CMV IE promoter" to "a CMV IE promoter," thus indicating that any CMV IE promoter is contemplated by the present invention.

Applicants note that all claim amendments made herein are supported by the Specification. Accordingly, Applicants respectfully request that the rejection of claims 1-15 under 35 U.S.C. §112, second paragraph, be withdrawn.

D. Rejection of Claims Under 35 U.S.C. §102(a), §102(e), and §103(a), are Overcome

1. Nature of the Rejections

Claims 1-15 are rejected under 35 U.S.C. §102(a) as being anticipated by, or in the alternative, under 35 U.S.C. §103(a), as being unpatentable over Nguyen *et al.* (Proc. Am. Assoc. Cancer Res. 37, #2370, March, 1996). Claims 1-16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (U.S. Patent No. 5,604,090) taken with Nguyen *et al.* Claims 1-15 are rejected under 35 U.S.C. §102(e) as being anticipated by, or in the alternative,

under 35 U.S.C. §103(a), as being unpatentable over Roth *et al.* (U.S. Patent No. 5,747,469). Claims 1-16 are rejected under 35 U.S.C. §103(a) as being unpatentable over Roth *et al.* taken with Alexander *et al.*

According to the Examiner, Nguyen *et al.* teaches that cisplatin (CDDP)-treated cells had 35% to 61% further inhibition of growth 3 days following p53 gene transfer compared to cells without CDDP treatment, and that Nguyen *et al.* also teaches the criticality of the timing of administration of a DNA-damaging agent relative to gene transfer. Alexander *et al.* is said to teach a method for enhancing expression of a transgene encoded by an adeno-associated virus (AAV) vector in dividing and non-dividing cells *in vitro*, the method comprising contacting a target cell with a DNA-damaging agent, washing the DNA-damaging agent-incubated cells with a buffer solution, and transferring said AAV vector into the cells after the washing step. Roth *et al.* is said to teach a method for killing tumor cells *in vitro* which comprises contacting a target tumor cell with a DNA-damaging agent, and transferring a vector comprising a CMV-IE promoter operably linked to a p53 encoded DNA to the tumor cell within about 12-24 hours after the contacting step. Roth *et al.* is also said to teach that where the DNA-damaging agent and p53 are applied separately to target cells, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell. Applicants respectfully traverse each of these rejections.

2. Nguyen et al. is Removed as a Reference Under 35 U.S.C. §102(a) and §103(a)

Applicants submit herewith a declaration submitted pursuant to *In re Katz*, 215 U.S.P.Q. 14 (C.C.P.A. 1928), establishing that Applicants are the sole inventors of the claimed subject

matter and that the reference of Nguyen *et al.* describes Applicants' own work (Appendix C). This declaration was originally submitted in response to a 35 U.S.C. §103(a) rejection during prosecution of the parent case, issued U.S. Patent No. 5,604,090 (filed June 6, 1994), to show that the reference describes the Applicants' own work, and to overcome Nguyen *et al.* as prior art under 35 U.S.C. §102(a).

Inventorship must be determined in light of the conception of the invention. *Sewall v. Walters*, 30 U.S.P.Q.2d 1356 (Fed. Cir. 1994). The declaration of Dr. Cristiano establishes that Applicants were solely responsible for the conception of the instant invention and are the sole inventors of the claimed subject matter.

Dr. Spitz and Dr. Kataoka were clinical fellows working under Dr. Cristiano's supervision and control, who were involved in the manipulation of animals used in that study. Dr. Wiehle was a Senior Research Associate, working under Dr. Cristiano's supervision and control, who was involved in animal manipulation and vector preparation. Dr. Roth was the head of the Department of Thoracic and Cardiovascular Surgery at M.D. Anderson, in which the reported study took place. None of these individuals contributed to the conception of the invention claimed in the instant patent application. Nguyen *et al.* is therefore removed as a §102(a) reference.

Applicants also respectfully requests the withdrawal of the rejections under §103(a) that relies wholly or in part on Nguyen *et al.* Regarding the rejection under §103(a) that relies wholly on Nguyen *et al.*, without the Specification, the information needed to practice the claimed invention would not be available to one of ordinary skill in the art. Regarding the rejection under §103(a) that relies on Alexander *et al.* taken with Nguyen *et al.*, Applicants assert that the rejection should be withdrawn since, as agreed by the Examiner on page 8, paragraph 2 of the

Office Action, Alexander *et al.* does not provide information pertaining to the timing requirement for transferring the transgene into the target cell.

3. Roth et al. is Removed as a Reference under 35 U.S.C. §103(a)

According to 35 U.S.C. §103(c), "[s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." Such a commonly owned reference is only disqualified when (1) the proper evidence is filed; (2) the reference only qualifies as prior art under 35 U.S.C. §102(f) or (g), or 35 U.S.C. §102(e) for applications filed on or after November 29, 1999, (*e.g.*, not 35 U.S.C. §102(a) or (b)) and (3) the reference was used in an obviousness rejection under 35 U.S.C. §103(a). *Manual of Patent Examining Procedure (MPEP)*, §706.02(l)(3).

Applicants assert that Roth *et al.* does not qualify as prior art under 35 U.S.C. §102(a) or (b). In accordance with the evidentiary requirements of *MPEP* § 706.02(l)(2), Applicants assert that Roth *et al.* and the instant application were, at the time the invention was made, subject to an obligation of assignment to the Board of Regents, The University of Texas System. In support of this assertion, Applicants herein submit the Declaration of Mr. Kevin Casement, Director of Technology Assessment and Licensing, MD Anderson Cancer Center (Houston, TX), under 37 C.F.R. §1.132 (Appendix D) to demonstrate that the instant application is subject to an obligation of assignment to the Board of Regents, The University of Texas System, and that Roth *et al.* was subject to an obligation of assignment to the same assignee at the time the invention was made.

In view of this declaration, Applicants assert that Roth *et al.* is not properly combinable as a reference under 35 U.S.C. §103(c), and that the rejection based on Roth *et al.* taken with Alexander *et al.* has been overcome since, as apparently agreed by the Examiner (Office Action, page 8, paragraph 2), Alexander *et al.* does not teach the timing limitation of the claimed invention.

4. Roth et al. is Not a Proper Reference Under 35 U.S.C. §102(e)

As discussed above, claims 1-15 are rejected under 35 U.S.C. §102(e) as being anticipated by Roth *et al.* Applicants assert that Roth *et al.* is not a proper reference under 35 U.S.C. §102(e) because the Examiner has not met the initial burden of showing how Roth *et al.* discloses the claimed invention, and because the claimed invention is patentably distinct over Roth *et al.*

Applicants first assert that that Examiner has not demonstrated how Roth *et al.* teaches the claimed invention. A rejection under 35 U.S.C. §102(e) requires that the Examiner specifically point out where Roth *et al.* teaches pre-administration of a DNA-damaging agent, transfer of a transgene following the pre-administration of a DNA-damaging agent, and the specifically claimed time interval between administration of a DNA-damaging agent and transfer of the transgene. The Examiner points to the following single passage:

> "[I]n embodiments where the DNA damaging factor and p53 are applied separately to the cell, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the DNA damaging agent and p53 would still be able to exert an advantageously combined effect on the cell. In such instances, it is contemplated that one would contact the cell with both agents within about 12-24 hours of each other." Office Action, page 10, paragraph 3, citing Roth *et al.*, Example 1, column 22.

The cited section of Roth *et al.* fails to clearly disclose the claimed sequence of events pertaining to initial administration of a DNA-damaging agent, followed by transfer of the transgene, and the specifically claimed time intervals between administration of the DNA-damaging agent and transfer of the transgene disclosed in the claimed invention.

Roth *et al.* appears to be more generic in the sense that the above cited passage indicates that the DNA damaging agent and p53 are "applied separately." In the invention disclosed herein, Applicants' claims are only directed to pre-administration of the DNA-damaging agent, and not administration of a DNA-damaging agent after transfer of the transgene. A genus does not always anticipate a claim to a species within the genus. See *MPEP* §2131.02, *Ex parte A*, 17 U.S.P.Q.2d 1716 (Bd. Pat. App. & Inter. 1990). However, when the species is clearly named, the species claim is anticipated. *Id.* Applicants assert that Roth *et al.* does not anticipate the claimed invention because the claimed invention is not sufficiently described in Roth *et al.* such that it is clearly named.

Applicants, without conceding that the claims as originally written were anticipated by Roth *et al.*, draw Examiner's attention to the amendment to the claims provided herein. Specifically, the amendment to the claims changes the timing limitation of claim 1 and dependent claims from "about 1-4 days" to "greater than about 1 day to less than or equal to 4 days." In addition, each of the new claims recites similar timing intervals that exclude exactly 24 hours from the time interval. Applicants assert that Roth *et al.* only teaches a timing interval of about 12-24 hours.

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art references." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Roth

et al. fails to anticipate the claimed invention because it does not teach a timing limitation of greater than about 1 day to less than or equal to 4 days.

A rejection based on 35 U.S.C. 102(e) can be overcome by persuasively arguing that the claims are patentably distinct over the prior art. *MPEP* §706.02(b). In view of the amendment to the claims, Applicants assert that their claims are clearly patentably distinct from the teachings of Roth *et al.* Therefore, Applicants assert that the rejection of claims 1-15 based on 35 U.S.C. §102(e) should be withdrawn.

5. The Rejections Under 35 U.S.C. §103(a) are Overcome

In applying an obviousness rejection, the references must be considered as a whole and must suggest the desirability, and thus the obviousness, of making the combination. *MPEP* §2141.01, citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986) (emphasis added). Further, in rejecting claims for obviousness, the prior art must be considered in its entirety. *MPEP* §2141.02.

As discussed above, Nguyen *et al.* is not a prior publication under §102(a), and Roth *et al.*, is not a proper §103(a) reference based on §103(c). The only remaining cited reference is Alexander *et al.* Alexander *et al.* has been overcome since, as apparently agreed by the Examiner (Office Action, page 8, paragraph 2), Alexander *et al.* does not teach the timing limitation of the claimed invention.

Even if Roth *et al.* were available as a reference under §103(a), Applicants assert that Roth *et al.* would not be render obvious the claimed invention. As discussed above, Roth *et al.*, does not teach the timing limitation of transferring the transgene into the dividing cell between

greater than about 1 day and less than or equal to 4 days after contacting said dividing cell with said DNA damaging agent. Therefore, the rejections under §103(c) are improper.

For all of the aforementioned reasons, Applicants respectfully submit that the rejections of the claims under 35 U.S.C. §102(a), §102(e), and §103(a) should be withdrawn.

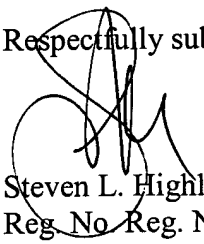
E. The Obviousness-Type Double Patenting Rejections are Overcome

Claims 1-15 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,271,207. Applicants will remove the issue of double patenting for claims 1-15 by filing a terminal disclaimer.

F. Conclusion

In view of the foregoing, it is believed that all claims are in condition for allowance, and a Notice of Allowance is earnestly solicited. The Examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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